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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/216,609	12/21/98	HANSEN H	018733/0734

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 08/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/216,609	Hanson, H.J.
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *May 30, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-54* is/are pending in the applicat

Of the above, claim(s) *47 and 48* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-46 and 49-54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 8, filed May 30, 2000, is acknowledged. Upon further consideration, Groups I through VI, as outlined in the restriction requirement mailed Mar. 29, 2000, are rejoined.

Applicant's election of species is acknowledged. Upon further consideration, the election of species requirement for element I, species of targeting proteins, is withdrawn.

Claims 47 and 48, drawn to non-elected species, are withdrawn from consideration.

Priority

2. The instant application claims priority, as a continuation-in-part, to copending application 08/445,110 (now U.S. Patent 5,851,527) filed May 19, 1995, which was a continuation of 07/182,623 (now abandoned) filed Apr. 18, 1988. The following claims of the instant application are drawn to inventions that are not supported by the disclosure of 08/445,110: claims 7-10, 12-15, 19, 21-30, 35, 37, 38, 40, 41, 45, 47, 48 and 54. For comparison with the prior art the filing date of the instant application, Dec. 21, 1998, will be used.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-50, 53 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 53 are vague and indefinite because of the recitation of optional steps "b" and "d" (for claim 1) and step "b" (for claim 53). It is not clear if steps "b" and "d" are necessary steps in the operation of the claimed methods.

Claim 2 is vague and indefinite because of the phrase "antibody subfragment. It is not clear how a subfragment of an antibody is different from a fragment of an antibody.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claims 1-50, 53 and 54 are drawn to methods for targeting a therapeutic agent to a target site in a patient. Claims 51 and 52 are drawn to kits and sterile injectable preparations for targeting a therapeutic agent to a target site in a patient. Thus, claims 1-54 read on methods of in vivo therapy and kits and preparations which may be used in such methods.

Claims 1-54 read on methods of in vivo therapy using immunotoxins for any type of disease. Thus, the nature of the claimed invention is unpredictable and that success in treating one type of disease is not necessarily predictive of success for a second type of disease (see Thorpe et al., U.S. Patent 6,036,955, column 2, lines 10-58).

The specification provides teachings to demonstrate how to make examples of the targeting constructs for converting prodrugs of anti-cancer drugs, but does not show data that use of the targeting constructs results in a therapeutic effect. Furthermore, the targeting constructs disclosed in the specification are not taught to be useful for diseases other than cancer.

All of the therapeutic agents contemplated in the specification operate by killing cells at the target site and are known, at least to be cytotoxic agents in vitro. However, because of the lack of working examples demonstrating the efficacy of the claimed methods, kits and preparations, it is not clear that, in vivo, that the localization to a target site of any of the contemplated cytotoxic agents would result in a therapeutic effect. Within the scope of the claimed methods is the treatment of a cancer which is often characterized by the presence of a solid tumor. The specification, while providing all of its examples for the formation of a targeting construct which might be suitable for the treatment of cancer, does not provide evidence that targeting of a cytotoxic agent would result in a decrease in tumor mass. Thus, while the targeting construct might successfully localize to a vascularized portions of a solid tumor, it is not clear that one of skill in the art would have a reasonable expectation of success in achieving a therapeutic effect if most of the solid tumor were poorly vascularized.

In view of the breadth of the claimed inventions, drawn to methods, kits and preparations, for the treatment of any disease using any type of therapeutic agent and in view of the inherent unpredictability of in vivo therapeutic methods and further in view of the lack of working examples, the claimed inventions are not commensurate in scope with the disclosure of the specification.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5,851,527. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49-53 are drawn to methods that are broader in scope than the methods claimed in U.S. Patent No. 5,851,527.

Claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49-53 of the instant application are drawn to methods which may or may not comprise administration of clearing agents. To the extent that claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49-53 read on methods that do not employ clearing agents the claims of the instant application are anticipated by the subject matter of the claims of U.S. Patent No. 5,851,527. To the extent that claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46, 49-53 read on methods that do employ clearing agents, the claims of

the instant application would be obvious over the subject matter of the claims of U.S. Patent No. 5,851,527 as evidenced by the disclosure of 5,851,527 (column 13, lines 44-56). Both sets of claims read on methods, kits and preparations useful for targeting cytotoxic agents to a target site.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 54 is rejected under 35 U.S.C. 102(b) as being anticipated by Bosslet et al (Bosslet, K. Cancer Research, 54, 2151-2159, 1994; IDS ref. "A29").

Claim 54 is drawn to a method for targeting a therapeutic agent to a target site comprising administering a fusion protein of the targeting protein and the enzyme.

Bosslet et al teaches a method of targeting a glucuronidase to a tumor bearing the CEA antigen employing a fusion protein consisting of a humanized CEA specific binding region and a human beta glucuronidase. Thus, Bosslet et al teaches a method that is the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 12, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma et al (Sharma, S.K. et al, Br. J. Cancer, 61: 659-662, 1990; IDS ref. "A28") in view of Martinis et al. (WO 83/03679, published Oct. 27, 1983).

Claims 12, 14 and 15 are drawn to methods for targeting a therapeutic agent to a target site comprising administering to the patient a multispecific targeting protein comprising at least one first binding site which specifically binds to a target site and a second binding site which specifically binds to a second binding site on an enzyme wherein the binding between the targeting protein and the enzyme does not interfere with enzyme activity; optionally administering a first clearing agent; administering an effective amount of the enzyme; optionally administering a second clearing agent; and administering a serum soluble prodrug composition wherein the enzyme acts on the prodrug to release a therapeutic agent that is less soluble in the serum than the prodrug and wherein the therapeutic agent accretes at the target site. The target site is the CEA antigen and the enzyme is CPG2.

Sharma et al teaches conjugates and methods for targeting the conjugates comprising an antibody fragment directed toward the CEA antigen and comprising the CPG2 enzyme. Sharma et al also teaches the use of a clearing agent, antibody SB43. Sharma et al does not teach methods employing targeting of enzyme to a target site using multispecific antibodies. However, Martinis et al teaches immunotherapeutic methods employing bispecific antibodies for the targeting of a cytotoxic agent to a target site (pages 6, lines 18- 28). Martinis et al further teaches that an advantage of using a bispecific antibody for delivery of toxic agents to a target site is that it reduces the possibility that the circulating target antigen will bind antibody bearing a substance lethal to tissue and deliver it to healthy tissues as can occur when the lethal agent is bound directly to a monospecific antibody directly to a monospecific antibody directed against the target antigen (page 33, lines 12 - 23). Thus, it would have been prima facie obvious to one of ordinary skill in the art that the method of Sharma et al could have been modified to use bispecific antibodies instead of chemical conjugation as a way of delivering an enzyme to a target site for the activation of a prodrug. One would have been motivated to have substituted bispecific antibodies for the chemical conjugate of Sharma et al in view of the teachings of Martinis et al on the advantages of bispecific antibodies instead of monospecific antibodies.

8. Claims 12, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996) in view of Martinis et al. (WO 83/03679, published Oct. 27, 1983).

The methods of claims 12, 14 and 15 have been discussed above. Because the claimed inventions are drawn to the optional administration of a clearing agent, references that teach methods without using clearing agents may also apply.

Blakey et al teaches conjugates and methods for targeting the conjugates comprising an antibody fragment directed toward the CEA antigen and comprising the CPG2 enzyme. Blakey et al does not teach methods employing targeting of enzyme to a target site using multispecific antibodies. However, as discussed above, Martinis et al teaches immunotherapeutic methods employing bispecific antibodies for the targeting of a cytotoxic agent to a target site (pages 6, lines 18- 28). Martinis et al further teaches that an advantage of using a bispecific antibody for delivery of toxic agents to a target site is that it reduces the possibility that the circulating target antigen will bind antibody bearing a substance lethal to tissue and deliver it to healthy tissues as can occur when the lethal agent is bound directly to a monospecific antibody directly to a monospecific antibody directed against the target antigen (page 33, lines 12 - 23). Thus, it would have been prima facie obvious to one of ordinary skill in the art that the method of Blakey et al could have been modified to use bispecific antibodies instead of chemical conjugation as a way of delivering an enzyme to a target site for the activation of a prodrug. One would have been motivated to have substituted bispecific antibodies for the chemical conjugate of Blakey et al in view of the teachings of Martinis et al on the advantages of bispecific antibodies instead of monospecific antibodies.

9. Claims 1, 2, 4, 5, 12, 14, 15, 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagshawe et al (Bagshawe, K.D. et al, Br. J. Cancer, 58: 700-703, 1988; IDS ref. "A21") in view of Martinis et al (supra) and further in view of Goldenberg (U.S. Patent 4,624,846, published Nov. 25, 1986).

Claims 1, 2, 5 are drawn to methods as outlined above for claims 12, 14 and 15 which depend from claim 1. Claim 2 limits the multispecific targeting protein to conjugates of antibodies and antibody fragments or subfragments. Claim 5 limits the enzyme to esterases, proteases, glucuronidases, dextranases, cellulases, and glycosidases. Claim 53 is drawn to a method similar to that of claim 1 except that the targeting composition is a targeting protein conjugated to a an enzyme.

Bagshawe et al teach a method of targeting a CPG2 enzyme to a target site bearing the beta hCG antigen. The prodrug used in a mustard-gluatamate prodrug. Bagshawe et al do not teach the use of multispecific targeting proteins. However, as discussed above, Martinis et al teaches immunotherapeutic methods employing bispecific antibodies for the targeting of a cytotoxic agent to a target site (pages 6, lines 18- 28). Martinis et al further teaches that an advantage of using a bispecific antibody for delivery of toxic agents to a target site is that it reduces the possibility that the circulating target antigen will bind antibody bearing a substance lethal to tissue and deliver it to healthy tissues as can occur when the lethal agent is bound directly to a monospecific antibody directly to a monospecific antibody directed against the target antigen (page 33, lines 12 - 23). Thus, it would have been prima facie obvious to one of ordinary skill in

the art that the method of Bagshawe et al could have been modified to use bispecific antibodies instead of chemical conjugation as a way of delivering an enzyme to a target site for the activation of a prodrug. One would have been motivated to have substituted bispecific antibodies for the chemical conjugate of Bagshawe et al in view of the teachings of Martinis et al on the advantages of bispecific antibodies instead of monospecific antibodies.

Bagshawe et al also fails to teach method employing clearing agents. However, Goldenberg discloses methods for enhancing target specificity of antibody localization comprising the use of antibodies specific for the target specific antibodies (abstract and column 2, lines 12-26). Thus, to the extent that claims 1, 2, 5, 12, 14, 15 and 53 read on methods employing clearing agents, it would have been prima facie obvious to one of ordinary skill in the art to have added steps to accelerate the clearance of the circulating forms of antibody conjugates given the teachings of Goldenberg.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
August 14, 2000

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